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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,329	03/05/2002	Tomomi Ikemoto	2645 USOP	7134
23115	7590	04/28/2004	EXAMINER	
TAKEDA PHARMACEUTICALS NORTH AMERICA, INC INTELLECTUAL PROPERTY DEPARTMENT 475 HALF DAY ROAD SUITE 500 LINCOLNSHIRE, IL 60069			TUCKER, ZACHARY C	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/070,329

Applicant(s)

IKEMOTO ET AL.

Examiner

Zachary C. Tucker

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 1-7 and 16-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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Lack of Unity of Invention

Applicants' election without traverse in the correspondence dated 13 April 2004, to prosecute the invention of Group II, claims 8-15 as was set forth in the Finding of Lack of Unity of Invention dated 16 March 2004 is noted.

The election is considered by the Office to have been made without traverse, as applicants have not pointed out any errors in the Finding of Lack of Unity of Invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8, 10, 11, 12, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the instantly claimed compounds wherein Y=acyl, does not reasonably provide enablement for compounds according to the above-indicated claims where Y=any and all conceivable electron-withdrawing groups. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Though a group of electron-withdrawing groups are described on page 14, lines 8-20 to page 15, lines 1-8 of the instant specification, syntheses of the claimed compounds are limited only to methods for making those claimed compounds where Y (the electron withdrawing group) is acyl (formyl).

The Wands Factors provide a guide for determining the scope of enablement:

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- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Each factor will be addressed.

(A) The compounds in claims 8, 10, 11, 12, 14 and 15 include compounds having the depicted molecular formulae. The substituent "Y" is extremely broad. The functional language recited to describe this substituent is contemplative of many different types of functional groups.

For example, trivalent boron atoms, with their empty *p*-orbital, are electron withdrawing groups, protonated amine and quaternary ammonium groups are electron withdrawing groups, an acetylene group, with its triple carbon-carbon bond is an electron withdrawing group, an oxime group, an azide group and many others are electron-withdrawing groups. None of these are described in the application, but are in fact claimed.

(B) Chemical compounds is the nature of the invention in claims 8, 10, 11, 12, 14 and 15.

(C) The state of the art is such that one synthetic method, in this case a method for making compounds according to the invention where Y= acyl is not broadly applicable to the synthesis of all compounds according to claims 8, 10, 11, 12, 14 and 15 where Y= any and all electron-withdrawing groups. The examples on pages 42-67 where the

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instantly claimed compounds are synthesized, rely on high (1N) concentrations of sodium hydroxide in one step, a catalytic hydrogenation in another step, two acidification steps with 6N hydrochloric acid, and a high temperature coupling reaction where sodium carbonate is employed. Boranes, ester groups, azides, oximes, and ammonium groups would simply not survive this series of chemical manipulations, at least for the reason that the required 1N sodium hydroxide, 6N HCl and catalytic hydrogenation would react with all of these functional groups. Boranes are Lewis acids which will react with a strong base, esters are hydrolyzed by strong bases, azides react with strong acids to form protonated amines, quaternary ammonium groups react would neutralize basic reagents with the strong positive charge on the nitrogen atom, acetylene groups would be partially chlorinated by the HCl employed in the reaction sequence, forming chloroethylenic groups, and oximes undergo hydrogenation reactions.

(D) The level of ordinary skill in the art with respect to the compounds according to claims 8, 10, 11, 12, 14 and 15 is that of a person with a graduate-level degree in organic chemistry, versed in synthetic methods.

(E) Chemical syntheses are not always predictable. However, one of ordinary skill in the art is able to predict in the instant case that the directions provided in the specification for making compounds according to instant claims 8, 10, 11, 12, 14 and 15 are not applicable to all compounds embraced by those claims.

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(F),(G) Direction provided for making compounds according to instant claims 8, 10, 11, 12, 14 and 15 is limited to the preparative examples, wherein synthesis of only compounds where Y=acyl is reported.

(H) The amount of experimentation necessary in order for one of ordinary skill in the art to realize a method of making all compounds falling within the scope of claims 8, 10, 11, 12, 14 and 15 is undue, because it necessitates that that person devise new synthetic schema. One cannot simply "plug in" to the synthetic method taught in the specification whichever starting material he wishes.

The directions provided in the specification for the compounds applicants wish to exclude others from making using and selling do not provide for synthetic methods necessary to make all of the claimed chemical compounds having a substituent at "Y" that withdraws electrons.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 8, the definition of substituents R², R³, R⁴, R⁵, R⁶, and R⁷, include "heterocyclic group" as one of the permissible identities. In claim 12, the definition of substituents R², R³, R⁴, and R⁵ include "heterocyclic group" as a claim limitation.

More than one definition of the general term "heterocyclic" or "heterocycle" is accepted by those of ordinary skill in the art of organic chemistry.

Some consider cyclic organic compounds wherein at least one carbon atom is replaced by sulfur, oxygen or nitrogen to be heterocyclic compounds, while others of ordinary skill include selenium, tellurium, boron or tin containing rings to be within the scope of the term "heterocyclic" as it is commonly used, and some definitions of "heterocyclic" do not require carbon to present at all.

The examiner directs applicants' attention to the following three references:

On page 200 of the McGraw-Hill Dictionary of Chemical Terms, the definition of "heterocyclic compound" is a compound in which the ring structure is a combination of more than one kind of atom.

On page 490 of the Concise Encyclopedia Chemistry, the definition of "heterocycles" is cyclic hydrocarbon compounds in which the ring consists of carbon and at least one other element, usually, N, O or S. The definition goes on to explain that the possibilities for synthesis are nearly unlimited, and that compounds wherein the heteroatoms are of elements like phosphorous, arsenic, selenium, and tellurium are being incorporated with increasing frequency.

On page 594 of Hawley's Condensed Chemical Dictionary, "heterocyclic" is defined as a closed-ring structure, usually, either 5 or 6 members, in which one or more of the atoms in the ring is an element other than carbon, *e.g.* sulfur, nitrogen, *etc.*

These three definitions should make it abundantly clear that there is not one specific and exact definition of the word "heterocyclic," thus when this term is present as

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a claim limitation, the metes and bounds of protection are not pointed out and distinctly claimed. Though the three above-cited definitions of the term have some shared aspects, chemists of ordinary skill would not necessarily agree on the metes and bounds of the term "heterocyclyl."

Applicants may argue that "heterocyclyl" has been fully defined in the specification, and therefore the requirements of 35 U.S.C. 112, second paragraph, have been met with respect to claim 14, substituents R₃ and R₄.

The examiner would respond by pointing out the fact that while it is proper to use the specification to interpret what the applicant meant by a word or phrase recited in the claim, it is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. See *In re Paulsen*; 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994); *Intervet America Inc. v. Kee-Vet Lab. Inc.*, 887 F.2d 1050, 1053, 12 USPQ2d 1474, 1476 (Fed. Cir. 1989).

Even if it were permissible to import subject matter from the specification into the instant claims, doing so would still render the claims indefinite. Definitions provided in the specification for the objected-to terminology, which appears on pages 19, 20 and the first line of page 21, are each prefaced with "may include" which is open-ended, nonlimiting and therefore does not point out and distinctly claim exactly which heterocyclic and aromatic heterocyclic groups are intended.

Also in claims 8 and 12, "optionally substituted" modifies every recited substituent besides "hydrogen atom" and "halogen atom." The term "substituted" does not point out and distinctly claim the subject matter applicants regard as the invention at least

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because which substituents are permitted and which are not permitted remains undefined. Because one of ordinary skill in the art can identify *some* of what is embraced by terminology does not prove that the metes and bounds of that term are clear to one of ordinary skill in the art.

In the absence of specific moieties intended to effectuate modification by "substitution" or attachment to the chemical core as claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein applicants fail to articulate by chemical name or structural formula, the particular moieties applicants regard as those which will facilitate substitution, requisite to identifying the composition of matter claimed.

As was explained *supra* regarding the definitions provided for "heterocyclic" in the instant specification, even if it were acceptable to import subject matter from the specification into the claims as claim limitations, doing so would still render the term "substituted" indefinite because the definitions of the term provided in the specification are always prefaced with "may include."

The terms "optionally substituted hydroxy group" and "optionally substituted thiol group" are particularly indefinite because neither of these functional groups is substitutable.

Because dependent claims 9-11 and 13-15 depend directly from claim 8 or claim 12, respectively, they are included in the rejection under this statute.

All of claims 9-11 and 13-15 recite the indefinite (as explained *supra*) language "optionally substituted" as well.

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Claim 8 is further indefinite because in that claim, the limitation, "or R¹ and R², R¹ and R⁴, R² and R³, R⁴ and R⁵, R² and R⁴, or R⁶ and R⁷ may form a ring" is specified. It is not clear from this recitation which kinds of ring are intended, if these substituents each form a separate ring, if these rings are permitted to be present all at the same time, or whether fused or spiro rings are intended by the claim language. Whether the rings incorporate, for example, sulfur, nitrogen or oxygen atoms is undefined. The size of the rings is not defined and whether or not the rings contain unsaturation is undefined.

Claim 12 is indefinite for the same reasons given in the preceding paragraph, except for R⁶ and R⁷, which are not present in claim 12.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

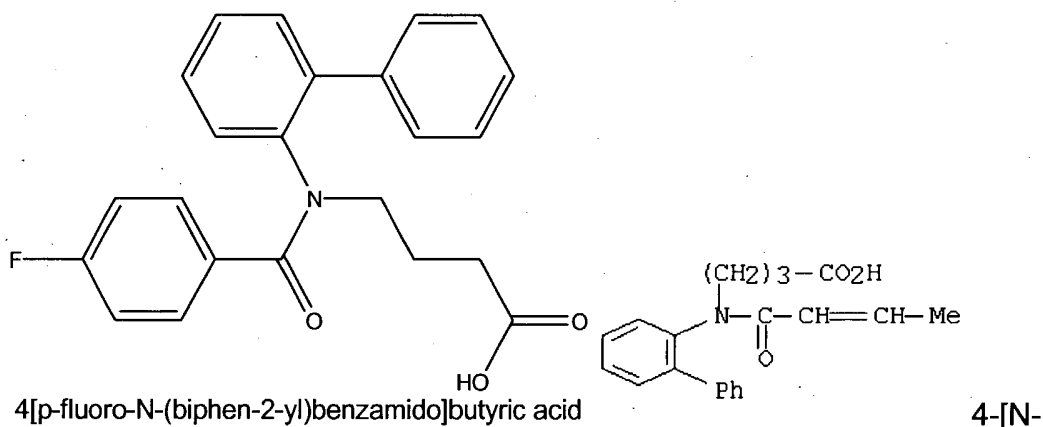
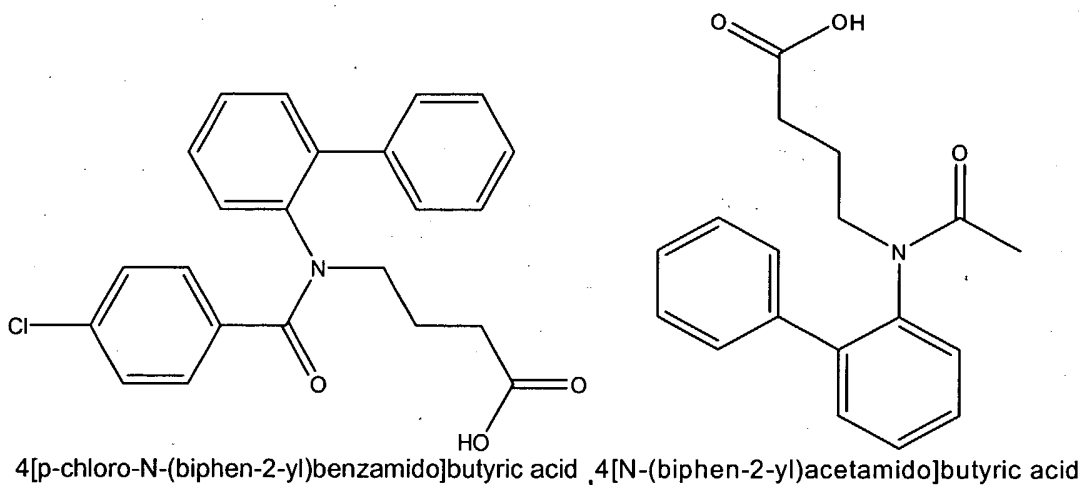
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 10, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by US 4,243,678 (Krastinat '678).

Krastinat '678 discloses in column 18, lines 45-48, the following four compounds

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(biphen-2-yl)crotonoylamido]butyric acid.

These are compounds according to instant claims 8, 10, 11, 12, 14 and 15 wherein Y is an aryl ring system, R¹ is an optionally-substituted acyl group, R², R³, R⁴, R⁵ are hydrogen atoms, (R⁶ and R⁷ in claim 8 form a benzene ring together).

Claims 8, 10, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by CA 1013960 (Lehman).

Page 4, line 60 of Lehman discloses 4-(N-2',6'-dichloroanilino)butyric acid sodium salt.

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This is a compound according to claims 8, 10, 11, 12, 14 and 15 wherein R^1 is an optionally substituted acyl group, Y is a chlorine atom, and R^2 , R^3 , R^4 , R^5 are hydrogen atoms, (R^6 and R^7 in claim 8 form a benzene ring together).

Claims 8, 10, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by GB 2 024 813 A (Krastinat et al).

Page 3 of Krastinat et al discloses several compounds according to instant claims 8, 10, 11, 12, 14 and 15.

These are:

4 - [4 - methoxy - N - (2' - fluoro - biphenyl - 2 - yl) - benzamido] - butyric acid,	
5 4 - [2, 4 - dichloro - N - (6 - methyl - biphenyl - 2 - yl) - benzamido] - butyric acid,	4 - [4 - chloro - N - (biphenyl - 2 - yl) - benzamido] - butyric acid,
4 - [N - (2' - ethyl - biphenyl - 2 - yl) - n - butyramido] - butyric acid,	4 - [N - (biphenyl - 2 - yl) - acetamido] - butyric acid,
4 - [3 - fluoro - 4 - methyl - N - (3, 2' - dimethyl - biphenyl - 2 - yl) - benzamido] - butyric acid,	4 - [4 - fluoro - N - (biphenyl - 2 - yl) - benzamido] - butyric acid,
	4 - [N - (biphenyl - 2 - yl) - crotonoylamido] - butyric acid,
	and

The compounds named above correspond with the structure specified in claims 8 and 12 as follows:

Y is a phenyl ring, R^1 is optionally-substituted acyl, R^2 , R^3 , R^4 , R^5 are hydrogen atoms, (R^6 and R^7 in claim 8 form a benzene ring together).

Claims 8, 10, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by

Berry, et al. "Polychloromatic Compounds. Part V. Preparation and Oxidation of Pentachlorophenyl-substituted Tertiary Amines and Reactions of n-Butyl-lithium and other Nucleophiles with various Pentachlorophenyl Derivatives" JOURNAL OF THE CHEMICAL SOCIETY 1285-1294(1969)

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... as cited by applicants.

Page 1292 of Berry et al reports a synthesis of N-formyl-N-pentachlorophenyl-4-aminobutanoic acid, which is a compound according to claims 8, 10, 11, 12, 14 and 15 where Y is a chlorine atom, R¹ is acyl, and R², R³, R⁴, R⁵ are hydrogen atoms, (R⁶ and R⁷ in claim 8 form a benzene ring together).

Claim Rejections - 35 USC § 103

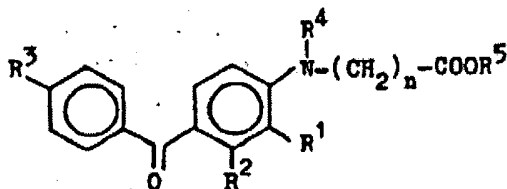
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 8, 10, 11, 12, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 237 918 (Englert).

At the time the invention was made, compounds according to claims 8, 10, 11, 12, 14 and 15 would have been obvious to one of ordinary skill in the art (an organic chemist skilled in the art of making pharmaceutical compounds) in view of the Englert publication.

Englert teaches compounds having the general formula (page 1):



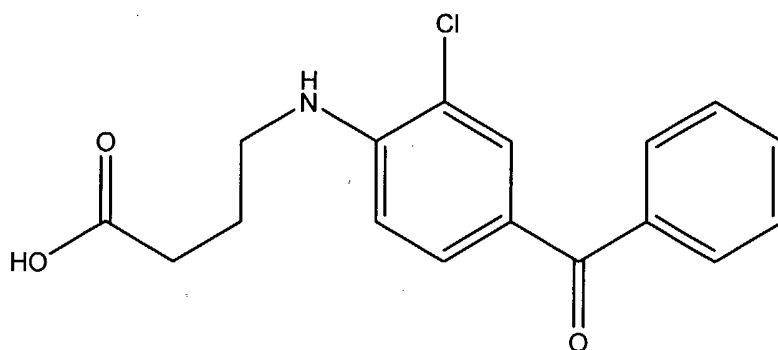
where R¹, R² and R³ are H, C₁-C₂ alkyl as well as halogen, R⁴ is H or C₁-C₄ alkyl and R⁵ is hydrogen or a salt-forming ion.

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The compounds are taught on page 1, lines 17-29, to be GABA (γ -aminobutyric acid) antagonists useful for treatment of diarrhea.

Six of the eight examples are butyric acid derivatives. Thus, $n=3$ is the preferred chain length in the generic formula I.

Example 7 on page 8 of Englert is a compound 4-(4-benzoyl-chloroanilino)butyric acid, which has this structure:



4-(4-benzoyl-2-chloroanilino)butyric acid

The deficiency of the Englert reference with respect to instant claims 8, 10, 11, 12, 14 and 15 is that no compound wherein the amino function, which corresponds to R^1 in those claims, bears "an optionally substituted hydrocarbon group, and optionally substituted acyl group, or an optionally substituted sulfonyl group," as required in instant claims 8, 10, 11, 12, 14 and 15, is exemplified.

Englert expressly suggests C_1 - C_4 alkyl at the R^4 position in generic formula I, depicted above.

The compound in Example 7, where the amino function bears a C_1 - C_4 alkyl substituent, therefore, is obvious because it is expressly suggested in Englert.

The motivation to make such a compound would have been to afford pharmaceutical products.

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Continuity

It is suggested that applicants amend the first line of the specification to note that the instant application was filed under 35 U.S.C. 371, and is the U.S. National Stage of PCT/JP00/06012, filed 5 September 2000.

Conclusion

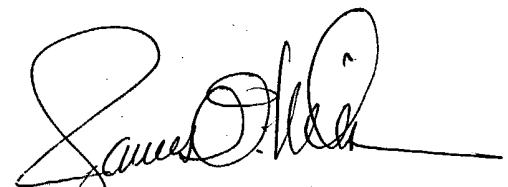
Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday-Friday from 6:30am to 3:00pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

If Dr. Shah cannot be reached, contact acting supervisor James O. Wilson at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-2717.

zt



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